free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

D6 $Cys-(Lys)_5-Cys$

s----------s (SEQ ID NO: 13).

Kindly add the following claim:

D7 63. (new) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of peptide:LPS where there is an excess of from 2 to 2500 times by weight of peptide, said peptide consisting essentially of:

(a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;

(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and (c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2.

64. (new) A vaccine for preventing gram-negative infections as defined in claim 63 which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of peptide:LPS where there is an excess of from 250 to 2500 times by weight of peptide.

REMARKS

In paragraph 1 of the Office Action, the request for a Continued Prosecution Application was accepted.

In paragraph 2 of the Office Action, the Amendment of May

8, 2001 was acknowledged and all rejections were withdrawn except for those discussed in the present Office Action.

In paragraph 3 of the Office Action, claims 25, 35, 39, 42-46, 49 and 50 were rejected under 35 U.S.C.§112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention.

Reconsideration is requested.

Claims 25, 35, 39, 42-46, 49 and 50 have been amended to be in independent form. For this reason the issue of proper dependency has been rendered moot and it is requested that this ground of rejection be withdrawn.

In paragraph 5 of the Office Action, the Examiner rejected claims 1-8, 10-17, 19-34, 51 and 57-62 under 35 U.S.C.§102(b) as being anticipated by Porro.

Reconsideration is requested.

process limitation

The Porro reference at page 7, lines 14-20 states that the vaccines may be made "using stoichiometric amounts of Lipid-A or LPS with the peptide". This does not disclose using a "stoichiometric excess of peptide relative to the lipid moiety" in the making of a vaccine which is the novel feature of applicant's vaccine.

In the Office Action, the Examiner noted that the claims did not recite: "stoichiometric excess of peptide relative to the lipid moiety" and that the Examiner did not suggest that phrase be added to the claims. At page 6, lines 11-23 of the present application, it was disclosed that Lipid A, which is present in all LPS', has a binding site which can be stoichiometrically saturated in vitro with certain peptides. However, it was discovered by the applicant that for the in vivo detoxification of LPS, it was necessary to use a stoichiometric excess of peptide relative to the amount of peptide which would stoichiometrically saturate the binding sites of LPS which are found on the Lipid A moiety.

This is a new novel way or improvement on process of preparing the vaccine, not the vaccine composition itself.

The stoichiometric excess required for the present invention has been expressed on a weight/weight basis based on the weight/weight ratio of LPS to the peptide. (page 6, lines

24-30 of the specification). While the term "stoichiometric" may be used to signify reactive quantities on a molar basis, the applicant has chosen to further define the invention using the weight ratio of the LPS to the peptide. In all cases where there is a stoichiometric excess of peptide relative to LPS, the peptide will be present in an amount which is in excess of the LPS on a weight/weight basis.

The average molecular weight for the peptide is 1,250 while the average molecular weight for Lipid A moiety of LPS is 1,700. Thus for the peptide of claim 36, a 1:1 mol/mol ratio corresponds to a 1:1.36 w/w ratio while a 2:1 mol/mol ratio corresponds to a 1.47:1 w/w ratio. Thus all of the claimed weight ratios of peptide: LPS are not anticipated or made obvious by the cited prior art which only discloses a stoichiometric ratio of 1:1.

The applicant believes that it is apparent from the language of Porro (which is the applicant's own patent) that the prior disclosure was of a procedure which a stoichiometric amount of peptide to Lipid A or LPS. The claims define a novel vaccine over the vaccine disclosed by Porro. In the absence of a disclosure of the presently claimed concept of using a stoichiometric excess of the peptide relative to LPS, it is submitted that the claims define novel subject matter and the rejection under 35 U.S.C.§102(b) should be withdrawn. In paragraph 6 of the Office Action, claims 1-8, 10-17, 19-34, 51 and 57-62 were rejected under 35 U.S.C.§103(a) as being unpatentable over Porro.

process limitations

Reconsideration is requested.

The Examiner is contending that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use whatever ratios of excesses of LPS and peptides since the determination of optimum concentrations of reactants is with the level of ordinary skill in the art. This is not the proper standard for the determination of obviousness. The determination of obviousness requires the identification of some direction or teaching in the prior art which can be relied upon as a basis for urging

that there was a "signpost" or "motivation" in the cited prior art that would cause the skilled worker in the art to make the novel contribution which is urged as the obvious deviation from the prior art. It is not proper to reject claims for obviousness by urging that "the determination of optimum concentrations of reactants... is within the level of ordinary skill in the art", when the prior art explicitly states what concentrations are to be used and gives no direction or information that would motivate a skilled artisan to change the ratio of peptide to LPS. Data appears in Fig. 1 of the present application which provides evidence of greatly increased efficacy when a vaccine made with 1:25 w/w of LPS to peptide is compared to a vaccine made with 1:250 w/w of LPS to peptide. This greater efficacy in reducing TNF production caused by an in vivo LPS challenge could not have been predicted from the prior art use of stoichiometric amounts of LPS and peptide as shown in the Porro reference. For these reasons, it is requested that this ground of rejection be withdrawn.

It has been noted that claims 52-56 have not been rejected and appear to be in condition for allowance. Claims 35 and 39 are believed to be in proper form and have not been amended. New claims 63 and 64 point out a preferred range of the amount of peptide that may be used in the invention.

Any fee which is required by this Amendment may be charged to Deposit Account No. 08-1540.

Early and favorable action is earnestly requested.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on 11/15/02

Marked up copy of amended claims:

25. (amended) A vaccine [as defined in claim 1 wherein] for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide [is of the formula] comprises: Cys-$(Lys-Phe-Leu)_3$-Lys-Cys
s----------s (SEQ ID NO: 20).

42. (amended) A vaccine [as defined in claim 1 wherein] for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide [is of the formula] comprises: ILe-Lys-Phe-Leu-Lys-Phe-Leu-Lys-Phe-Leu-Lys (SEQ ID NO: 37).

43. (amended) A vaccine [as defined in claim 1 wherein] for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide [is of the formula] comprises: Lys-Phe-Leu-Lys-Phe-Leu-Lys (SEQ ID NO: 38).

44. (amended) A vaccine [as defined in claim 1 wherein] for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide [is of the formula] comprises: Arg-Tyr-Val-Arg-Tyr-Val-Arg-Tyr-Val (SEQ ID NO: 39).

45. (amended) A vaccine [as defined in claim 1 wherein] for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide [is of the formula] comprises: Lys-Phe-Phe-Lys-Phe-Phe-Lys-Phe-Cys (SEQ ID NO: 40).

46. (amended) A vaccine [as defined in claim 1 wherein] for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide [is of the formula] comprises: Ile-Lys-Phe-Leu-Lys-Phe-Leu-Lys-Phe-Leu (SEQ ID NO: 41).

50. (amended) A vaccine [as defined in claim 1 wherein] for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide [is of the formula] comprises: Lys-Arg-Leu-Lys-Trp-Lys-Trp-Lys-Gly-Lys-Phe (SEQ ID NO: 45).

55. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

$Cys-(Lys)_5-Cys$

s----------s (SEQ ID NO: 13).